

**OFFICE OF VACCINES
RESEARCH AND REVIEW**
**Center for Biologics Evaluation
and Research**

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Division of Viral Products

Laboratory Mission and Function

- Ensure the safety and efficacy of vaccines and related biological products for human use
 - Bacterial vaccines
 - Viral vaccines
 - Parasitic vaccines
 - Allergenic products
- Facilitate the development, evaluation, licensure and use of new vaccines and related products that positively impact the public health

Laboratories in the Office of Vaccines Research and Review

- **Immediate Office of the Director**
 - Standards and Testing Section
 - Analytical Chemistry Staff
- **Division of Viral Products**
 - Laboratories of DNA Viruses, Retrovirus Research, Hepatitis Viruses, Vector-Borne Viral Diseases, Immunoregulation, Method Development, Respiratory Diseases
- **Division of Bacterial, Parasitic and Allergenic Products**
 - Laboratories of Immunobiochemistry, Biophysics, Enteric & Sexually Transmitted Diseases, Bacterial Polysaccharides, Methods Development & Quality Control, Mycobacterial Diseases & Cellular Immunology, Bacterial Toxins, Respiratory & Special Pathogens

Facilitating the Development and Evaluation of New Vaccines

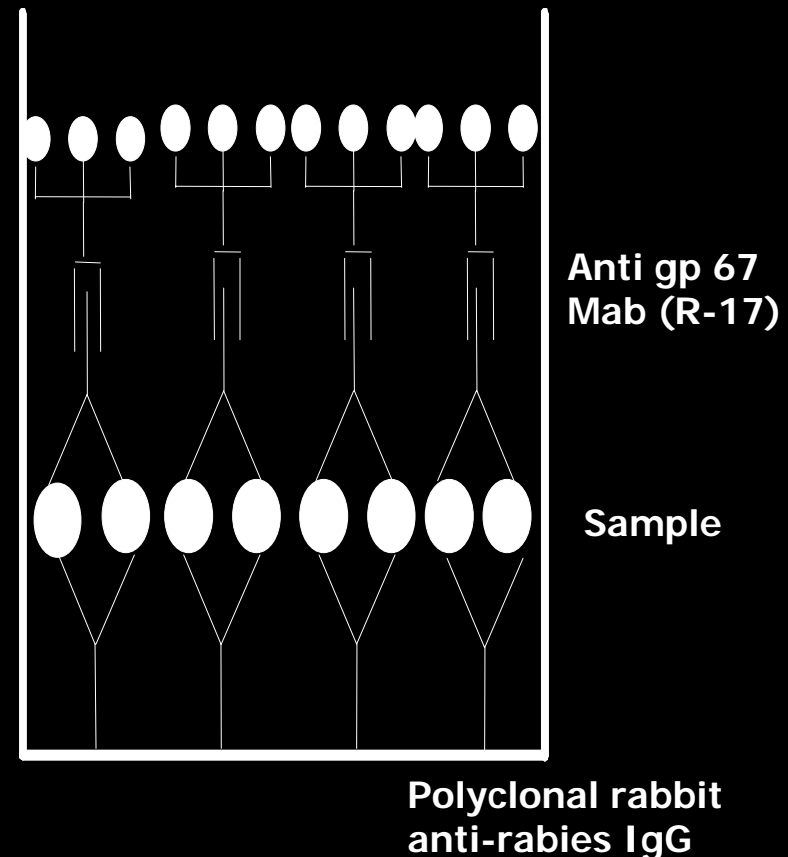
- **Anticipating and Addressing the Regulatory Issues for New Products**
 - General regulatory issues applicable to many products or product classes
 - Cell substrate issues
 - Improved test methods (sensitivity, reliability, etc.)
 - Product specific issues
 - Correlates of protection necessary for efficacy evaluation
 - Improved assays (e.g., potency, efficacy)
 - Animal models for efficacy evaluation
- **Prioritizing Research Efforts**
 - Availability of necessary expertise
 - Appropriateness of research effort
 - Competing demands

Development of Alternative Lot Release Tests for Vaccines

- **Increased product availability**
 - Emergency situations
 - Standardize requirements for new products
- **Aid development of combination products**
- **Reduce animal testing**
 - Test uncertainties
 - Costs, difficulties
- **Recent vaccine examples**
 - Rabies potency
 - Mumps neurovirulence,
 - Anthrax potency
 - Diphtheria toxoid potency

New Improved Rabies Potency Test

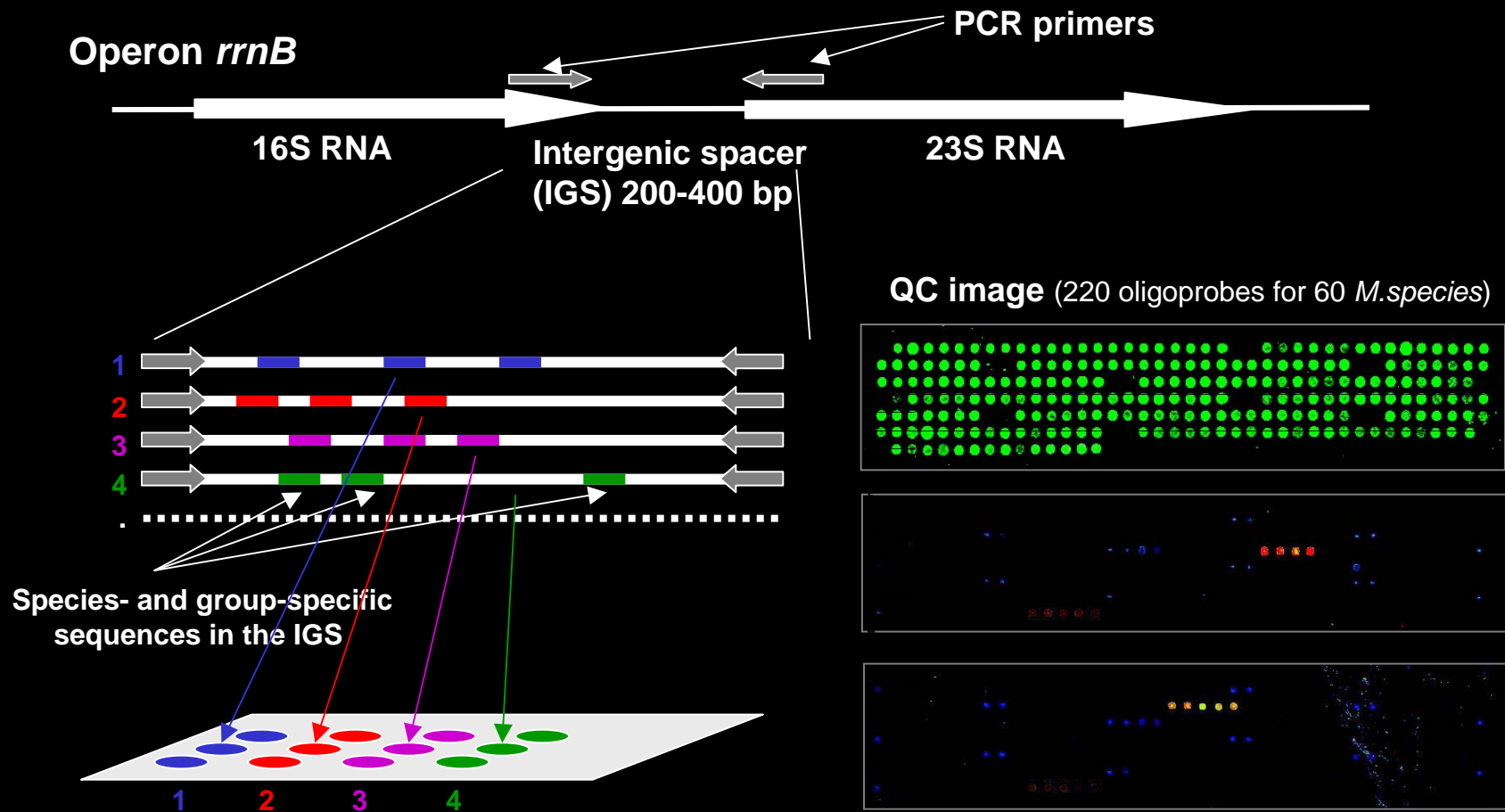
- **Current potency test**
 - Animal protection assay
 - ~600 mice per test
 - ~6 weeks per assay
 - High degree of variability (25-400%)
- **Alternative assay**
 - Capture ELISA
 - R-17 recognizes neutralizing epitope and is conformation dependent



Development of Rapid Microbial Tests

- New microbial tests would foster improvements in current products and facilitate development and evaluation of new vaccine products
- Current tests for are culture based, lengthy, and require large volumes
 - Bacteria, Fungi, Molds (≥ 14 days)
 - Direct inoculation (FTM & SCDM or TSB)
 - Membrane filtration
 - Mycoplasma (≥ 21 days)
 - Agar and broth culture based
 - Complex media
 - Limited shelf life

Microarray-Based Assay for Detection of *Mycoplasma*, *Spiroplasma*, and *Ureaplasma* Species



Use of Novel Cell Substrates for Vaccine Production

- The use of novel cell substrates (poorly characterized, transformed, neoplastic cells, etc.) for vaccine production presents several regulatory concerns including:
 - Potential presence of adventitious agents that can be present in vaccines
 - New molecular methods under development to detect broad categories of potential adventitious agents
 - Theoretical oncogenic risk
 - Development of new assays to define the oncogenic potential of residual DNA from tumorigenic or tumor-derived cells
 - Evaluation of in vivo methods to detect known oncogenic viruses

New Smallpox Vaccines

- **Development and Licensure of New Smallpox Vaccines Became a High Priority for Public Health Agencies in 2001**
 - Issues regarding the safety of such vaccines include adverse events associated with traditional vaccines (e.g., neurovirulence, myocarditis, progressive vaccinia, eczema, etc.)
 - Issues regarding efficacy evaluation of new products include:
 - Evaluation of efficacy in the absence of disease
 - Determination and evaluation of relevant animal models for efficacy
 - Role and contribution of individual vaccine antigens
 - Appropriate measures of immunogenicity and protection for new vaccines (e.g. correlates of protection)
 - Improved assays for measurement in clinical trials and in animal models

Improved Assays for Evaluation of New Smallpox Vaccines

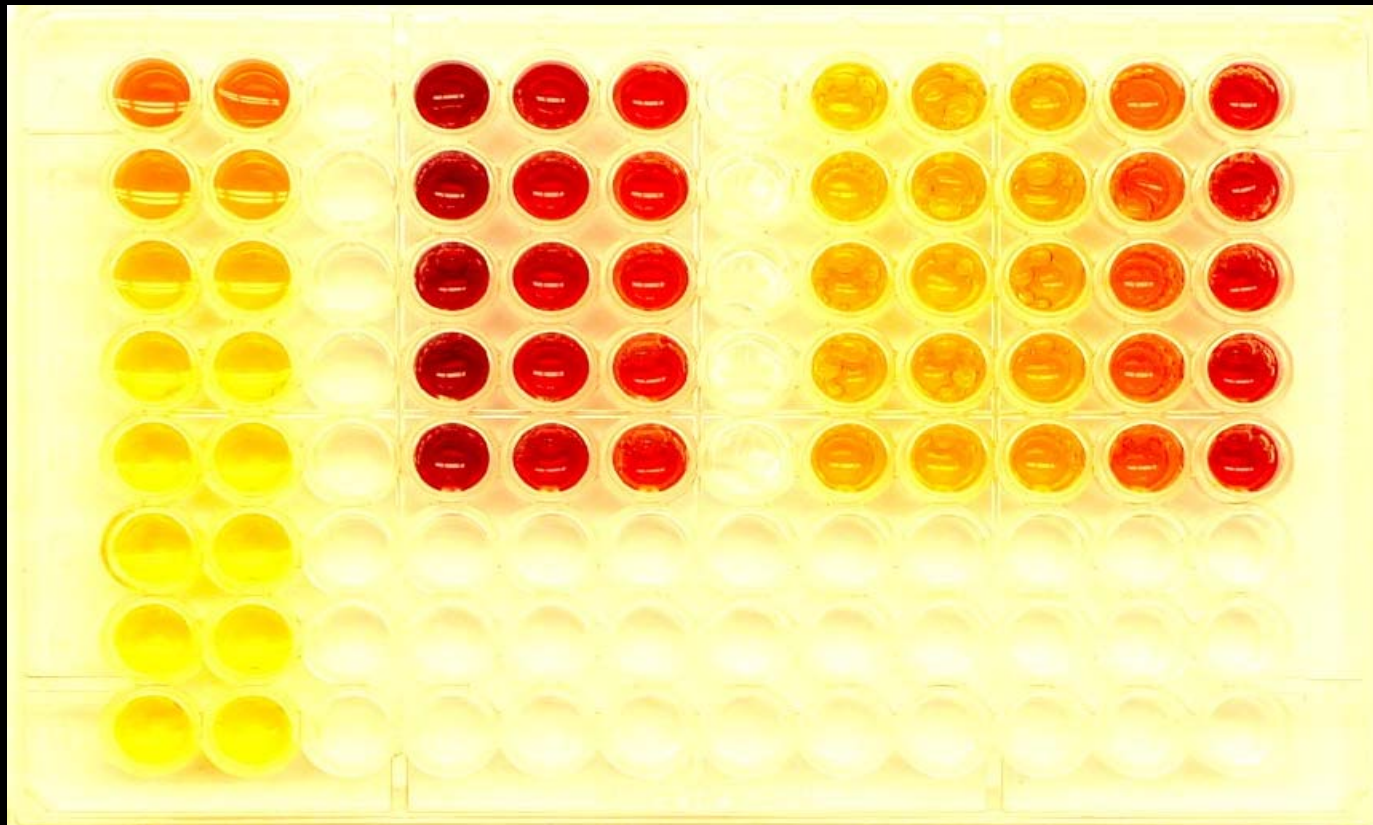
- **Identification of Research Issues**
 - One of the rate limiting steps in new vaccine development was the need for a high throughput, precise and reproducible method for measuring the neutralizing antibody response in vaccines
 - Initiation of smallpox vaccination would require increased production and use of Vaccinia-IgG (VIG), the only therapy available for treatment of vaccine adverse events. New methods were needed for measuring the strength and shelf-life of VIG preparations

HIGH THROUGHPUT VACCINIA NEUTRALIZATION ASSAY BASED A REPORTER GENE READOUT

β -Gal
Standards

Virus Titration
0.12 0.06 0.03

Virus-Neutralization
Anti-vaccinia IgG (VIG)



Other Examples of Critical Path Efforts for Priority Viral Vaccines

- **Hepatitis C**
 - Development of transgenic mouse models to study pathogenesis and evaluate candidate vaccines
- **HIV**
 - Development of new serodetection EIA for differential diagnosis of HIV infections in the presence of vaccine-generated antibodies
 - Identification of target structures and epitopes for neutralizing antibodies
- **West Nile Virus**
 - Development of standardized immunological assays for vaccine induced immunity
- **Poliovirus Vaccines**
 - Development of animal models to evaluate efficacy of Sabin-derived IPV
- **Influenza Vaccines**
 - Development and standardization of reference strains and reagents for evaluation of pandemic influenza vaccines for pandemic influenza

Neisseria Meningitidis

Goals of the Meningitis Vaccine Project



PATH



- Goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa (1997 ~ 200,000 cases, 15% CFR)
 - Be immunogenic in young children
 - Induce long term protection
 - Induce herd immunity

Neisseria Meningitidis

Critical Path of the Meningitis VP



Other Examples of Critical Path Efforts for Priority Bacterial Vaccines

- **Anthrax**
 - Development of animal models of pathogenesis
 - Development of serological assays
 - Development of Ty21a vector for PA
 - Establish tools for genetic manipulation of the pathogen
- **Tuberculosis**
 - Discovery of novel antigens with protective properties
 - Evaluation of DNA vaccines
- **Shigella**
 - Creation of Ty21 vector of shigella LPS
- **Pneumococcus**
 - Identification of serological correlates of protection
- **Meningitis**
 - Development of high-efficiency conjugation technology
 - Establishment of correlates of protection

Summary and Future Directions

- Numerous scientific, technical, and regulatory challenges must be addressed in the development of new and improved vaccines
 - General regulatory issues
 - Product specific issues
 - Challenge of vaccine development for emerging diseases
- OVRP researcher/reviewers have a major role in identifying and anticipating such issues
 - Clear guidance regarding expectations for product development and licensure
 - Guidance documents (e.g., revised cell substrate and DNA vaccines guidance)
 - CBER research activities necessary to address certain issues with regulatory implications
 - Product development
 - Product evaluation

A Comment on Moving Forward

Nothing would be done at all if one waited until one could do it so well that no one could find fault with it.

- John Henry Cardinal Newman